Search Strategy

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     FILE 'MEDLINE, USPATFULL, WPIDS'
                E POIRIER JUDES/AU
                E POIRIER J/AU
L1           211 FILE MEDLINE
L2             0 FILE USPATFULL
L3            25 FILE WPIDS
     TOTAL FOR ALL FILES
L4           236 S E3
L5            13 FILE MEDLINE
L6             0 FILE USPATFULL
L7             2 FILE WPIDS
     TOTAL FOR ALL FILES
L8            15 S L4 AND (APOE? OR APOLIPOPROTEIN)
L9         12021 FILE MEDLINE
L10          310 FILE USPATFULL
L11          171 FILE WPIDS
     TOTAL FOR ALL FILES
L12        12502 S APOLIPOPROTEIN
L13           90 FILE MEDLINE
L14            3 FILE USPATFULL
L15            0 FILE WPIDS
     TOTAL FOR ALL FILES
L16           93 S L12 AND ALZHEIMER? DISEASE
L17           18 FILE MEDLINE
L18            3 FILE USPATFULL
L19            0 FILE WPIDS
     TOTAL FOR ALL FILES
L20           21 S L16 AND (DIAGNOS? OR PROGNOS?)
                E SCHMECHEL DONALD E/AU
L21            0 FILE MEDLINE
L22            1 FILE USPATFULL
L23            0 FILE WPIDS
     TOTAL FOR ALL FILES
L24            1 S E3
L25            1 FILE MEDLINE
L26            0 FILE USPATFULL
L27            0 FILE WPIDS
     TOTAL FOR ALL FILES
L28            1 S L16 AND CHOLINOMIMETIC?
L29         3276 FILE MEDLINE
L30          227 FILE USPATFULL
L31           71 FILE WPIDS
     TOTAL FOR ALL FILES
L32         3574 S APOE?
L33            3 FILE MEDLINE
L34            0 FILE USPATFULL
L35            1 FILE WPIDS
     TOTAL FOR ALL FILES
L36            4 S L32 AND PRION?
L37            6 FILE MEDLINE
L38            0 FILE USPATFULL
L39            0 FILE WPIDS
     TOTAL FOR ALL FILES
L40            6 S L32 AND CREUTZFELDT-JAKOB
L41           16 FILE MEDLINE
L42            3 FILE USPATFULL
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L43           0 FILE WPIDS
     TOTAL FOR ALL FILES
L44          19 S L32 AND (AMINO ACID METABOLISM)
L45           0 FILE MEDLINE
L46           0 FILE USPATFULL
L47           0 FILE WPIDS
     TOTAL FOR ALL FILES
L48           0 S L44 AND CONGENITAL DEFECT?
L49           0 FILE MEDLINE
L50           0 FILE USPATFULL
L51           0 FILE WPIDS
     TOTAL FOR ALL FILES
L52           0 S L32 AND FRAGILE-X SYNDROME
L53        1764 FILE MEDLINE
L54           9 FILE USPATFULL
L55          25 FILE WPIDS
     TOTAL FOR ALL FILES
L56        1798 S FRAGILE-X SYNDROME
L57           1 FILE MEDLINE
L58           1 FILE USPATFULL
L59           0 FILE WPIDS
     TOTAL FOR ALL FILES
L60           2 S L56 AND APOLIPOPROTEIN
L61           0 FILE MEDLINE
L62           0 FILE USPATFULL
L63           0 FILE WPIDS
     TOTAL FOR ALL FILES
L64           0 S L32 AND HUNTINGTON? DISEASE
L65         453 FILE MEDLINE
L66          22 FILE USPATFULL
L67          22 FILE WPIDS
     TOTAL FOR ALL FILES
L68         497 S HUNTINGTON? DISEASE
L69          14 FILE MEDLINE
L70           4 FILE USPATFULL
L71           0 FILE WPIDS
     TOTAL FOR ALL FILES
L72          18 S L68 AND REVIEW?
L73          46 FILE MEDLINE
L74           6 FILE USPATFULL
L75           1 FILE WPIDS
     TOTAL FOR ALL FILES
L76          53 S L68 AND PATHOLOGY
L77           7 FILE MEDLINE
L78           0 FILE USPATFULL
L79           0 FILE WPIDS
     TOTAL FOR ALL FILES
L80           7 S L76 AND PATHOGENESIS
L81          15 FILE MEDLINE
L82           0 FILE USPATFULL
L83           0 FILE WPIDS
     TOTAL FOR ALL FILES
L84          15 S L32 AND (PRESENILIN OR SENILIN)
L85           1 FILE MEDLINE
L86           1 FILE USPATFULL
L87           0 FILE WPIDS
     TOTAL FOR ALL FILES
L88           2 S L16 AND APOC?
L89           1 FILE MEDLINE
L90           1 FILE USPATFULL
L91           0 FILE WPIDS
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	TOTAL FOR ALL FILES	
L92	2	S ALZHEIMER? DISEASE AND APOC?
L93	2334	FILE MEDLINE
L94	669	FILE USPATFULL
L95	395	FILE WPIDS
	TOTAL FOR ALL FILES	
L96	3398	S NEUROLOGICAL DISORDERS
L97	4	FILE MEDLINE
L98	3	FILE USPATFULL
L99	0	FILE WPIDS
	TOTAL FOR ALL FILES	
L100	7	S L96 AND MOLECULAR GENETICS
L101	109	FILE MEDLINE
L102	51	FILE USPATFULL
L103	1	FILE WPIDS
	TOTAL FOR ALL FILES	
L104	161	S L96 AND PATHOGENESIS
L105	11	FILE MEDLINE
L106	26	FILE USPATFULL
L107	0	FILE WPIDS
	TOTAL FOR ALL FILES	
L108	37	S L101 AND REVIEW?

L7 ANSWER 1 OF 2 WPIDS
AN 95-383002 [49] WPIDS
DNC C95-165565
TI Selecting Alzheimer's disease patients likely to respond to cholinomimetic therapy - on the basis of apo-lipoprotein E alleles present, the E4 allele, associated with loss of cerebral acetyl-choline synthesis, indicating a poor result.
DC B04 D16
PA (MART-N) MARTINEX R & D INC

AB **WO 9529257** A UPAB: 951211
Treatment of Alzheimer's disease (AD) in patients genetically characterised as likely to respond to cholinomimetic therapy comprises: (1) determining presence of ***apolipoprotein*** (apo) E2 and E3 alleles, or the absence of apo E4 alleles, in peripheral tissue, indicative of the degree of impairment of cerebral acetylcholine (ACL) synthesis and nicotinic receptor activity and (2) admin. a suitable therapeutic agent (I) according to the measured degree of impairment. Also claimed is a process for identifying humans with cognitive impairment (due to age, AD or other neurodegenerative diseases) who are likely to respond to treatment with cholinomimetics (or cognitive enhancers) based on analysis of ***apoE*** alleles as above.
USE - The method allows AD or other patients who are likely to benefit from cholinomimetic therapy to be identified. It is based on the observation that presence of the apo4 allele is associated with a marked redn. in residual choline acetyltransferase, apparently as a selective loss of ACh-synthesising neurons in the nucleus basalis of Maynert and the diagonal band of Broca.
Dwg.8A/8

L7 ANSWER 2 OF 2 WPIDS
AN 95-231581 [30] WPIDS
DNC C95-106931
TI Diagnosis and prognosis of Alzheimer's disease - by determining the number of copies of ***apoE*** gene allele E4 in a sample from a patient.
DC B04 D16
PA (POIR-I) POIRIER J; (UYMC-N) UNIV MCGILL

AB **WO 9516791** A UPAB: 950804
A method (A) for the clinical determn. of the risk for the late-onset of Alzheimer's disease (AD) or for diagnosing or prognosing AD in a patient comprising: (a) amplifying genomic DNA encoding ***apoE*** in a biological sample of the patient using oligonucleotide (ON) primers specific to E2, E3 or E4; and (b) determining the number of copies of the ***apoE*** gene allele E4 in the biological sample, whereby one or two copies indicates: (i) a level of incidence of late-onset of AD and a lowered age of death; or (ii) that the patient is afflicted with or at risk of developing AD with a lowered age of death. Also claimed is a method (B) for the clinical determn. of the risk for the late-onset of AD for diagnosing or prognosing AD in a patient which comprises (A) amplifying genomic DNA encoding apo E in a biological sample of the patient using ON primers specific to a region of the ***ApoE*** gene common to ***apoE2*** , ***apoE3*** and ***apoE4*** alleles and (b) genotyping the patient's ***apoE*** isoforms by DNA sequencing the amplified DNA for indirectly determining the number of copies of the ***apoE*** gene allele E4 in the sample, whereby one or two copies of E4 indicates a level of incidence of

late-onset of AD and a lowered age of death.

USE - The determn. of the ***apoE4*** allele copy numbers allows for the determn. of the extent of the risk of having AD, the prediction of the age of death of a patient and the diagnosis of AD. Dwg.0/4

L5 ANSWER 10 OF 13 MEDLINE
93382172 ***Apolipoprotein*** E polymorphism and Alzheimer's disease [see comments]. ***Poirier J*** ; Davignon J; Bouthillier D; Kogan S; Bertrand P; Gauthier S. (McGill Centre for Studies in Aging, Douglas Hospital Research Centre, Verdun, Quebec, Canada..)LANCET, (1993 Sep 18) 342 (8873) 697-9. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB ***Apolipoprotein*** E (***apoE***) is associated with Alzheimer's neurofibrillary tangles and beta-amyloid protein in senile plaques. It also appears to play an important part in the redistribution of lipids that follows deafferentation and neurodegeneration in the brain. The gene for ***apoE*** is on chromosome 19, within the genomic region previously associated with late-onset familial Alzheimer's disease (AD). We have studied ***apoE*** phenotype expression and the corresponding allele frequencies (epsilon 2, epsilon 3, epsilon 4) in 91 patients with sporadic AD and 74 controls. There was a significant association between epsilon 4 and sporadic AD (epsilon 4 frequency 0.380 in AD and 0.122 in controls, $p < 0.01$). Analysis of epsilon 4 in whom AD develops this tended to happen earlier in life than in those with epsilon 3 or epsilon 2. The epsilon 4/AD association was more pronounced in women. Octogenarians with AD had an epsilon 4 allele frequency that was 3 times higher than one reported, in a different study, in healthy octogenarians. ***ApoE*** may be an important susceptibility factor in the aetiopathology of sporadic AD.

L5 ANSWER 1 OF 13 MEDLINE
97146633 ***Apolipoprotein*** E genotype and gender influence response to tacrine therapy. Farlow M R; Lahiri D K; ***Poirier*** *** J*** ; Davignon J; Hui S. (Department of Neurology, Indiana University School of Medicine, Indianapolis 46202-5111, USA.)ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1996 Dec 16) 802 101-10. Journal code: 5NM. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Our objective is to evaluate the effects of ***apolipoprotein*** E genotype (***APOE***) on clinical response to treatment with tacrine, in patients with Alzheimer's disease (AD). Only 25 to 50% of patients with AD, depending on dose and design, have been responders in previous tacrine trials. AD autopsy studies have suggested that ***APOE*** epsilon 4 is associated with decreased numbers of cholinergic markers in temporal cortex and the hippocampus. Our hypothesis was that cholinergic therapy might be less effective in epsilon 4 carriers. ***APOE*** phenotypes were determined from plasma samples previously saved from a large 30-week, randomized, double-blind placebo-controlled, parallel-group, multicenter trial of tacrine at dosages of 80, 120, or 160 mg/day. Outcome measures included Alzheimer's Disease Assessment Scale (ADAS) and its cognitive component (ADAS-Cog), Clinician's Interview-Based Impression (CIBI), Global Deterioration Scale (GDS), and the caregiver-rated Clinical Global Impression of Change (CGIC). Analyses were performed on the change in scores from baseline to last observation on 460 patients having ***APOE*** results available. There were 291 patients heterozygous or homozygous for ***APOE*** epsilon 4 and 169 patients with only ***APOE*** epsilon 2 or epsilon 3 alleles. Analysis of variance showed non- ***APOE*** epsilon 4 carriers (E2,3) on tacrine improved more versus placebo than patients with ***APOE*** epsilon 4 (E4) on tacrine versus placebo as measured by the ADAS (p

= 0.04) and the ADAS-Cog (p = 0.05). A trend toward greater treatment effect in the E2,3 patients was seen with CIBI, GDS, and CGIC, but these differences did not achieve significance. ***APOE*** genotype may be a predictor for clinical response to tacrine in AD patients, ***APOE*** epsilon 4 associated with a lower probability of cognitive improvement. When the groups were further divided by gender, most of the effect of ***APOE*** on treatment response was seen in women. E2-3 women improved more than any other group, and E4 women the least. The interaction of gender and ***APOE*** genotype on treatment response as measured by ADAS-Cog was significant (p = 0.03). Future trials of cholinergic therapy in AD should include ***APOE*** genotyping.

L5 ANSWER 2 OF 13 MEDLINE
96417388 ***Apolipoprotein*** E in the brain and its role in Alzheimer's disease. ***Poirier J*** . (Douglas Hospital Research Centre, Verdun, Quebec, Canada.)JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, (1996 Mar) 21 (2) 128-34. Journal code: A0C. ISSN: 1180-4882. Pub. country: Canada. Language: English.

AB Recent evidence indicates that ***apolipoprotein*** E (***apoE***) plays a central role in the brain response to injury. The coordinated expression of ***apoE*** and its main receptor, the ***apoE*** /apoB (LDL) receptor, appears to regulate the transport of cholesterol and phospholipids during the different phases of the reinnervation process. The recent discovery that a peculiar form of ***apoE*** , the ***apoE4*** , is strongly linked to both sporadic and familial late onset Alzheimer's disease (AD) raises the possibility that a dysfunction of the lipid transport system associated with compensatory sprouting and synaptic remodelling could be central to the AD process. The role of ***apoE*** in the central nervous system (CNS) is particularly important in relation to the function of the cholinergic system which relies to a certain extent on the integrity of phospholipid homeostasis in neurons. Recent evidence suggests that ***apoE4*** allele has a direct impact on cholinergic function in AD.

L5 ANSWER 3 OF 13 MEDLINE
96371124 Association of ***apolipoprotein*** E genotype with brain levels of ***apolipoprotein*** E and ***apolipoprotein*** J (clusterin) in Alzheimer disease. Bertrand P; ***Poirier J*** ; Oda T; Finch C E; Pasinetti G M. (Centre for Studies in Aging, McGill University, Montreal, Que, Canada.)BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1995 Oct) 33 (1) 174-8. Journal code: MBR. ISSN: 0169-328X. Pub. country: Netherlands. Language: English.

AB This study examines the relationship between the levels of ***apolipoprotein*** E (***apoE***) and ***apolipoprotein*** J (apoJ, also designated as clusterin) as a function of ***apoE*** genotype in the hippocampus and cortex of Alzheimer disease (AD) subjects. These two lipophilic proteins which are involved in the maintenance of lipid homeostasis are both synthesized in the brain by astrocytes. Results indicate a reduction of ***apoE*** levels in the hippocampus and frontal cortex that is proportional to the ***apoE4*** allele dose. Conversely, apoJ (clusterin) levels were found to increase proportionately to the number of ***apoE4*** allele dose. These results suggest a compensatory induction of apoJ (clusterin) in the brain of ***apoE4*** AD subjects showing low brain levels of ***apoE*** .

L5 ANSWER 4 OF 13 MEDLINE

96262754 ***Apolipoprotein*** E, synaptic plasticity and Alzheimer's disease. ***Poirier J*** ; Minnich A; Davignon J. (Department of Psychiatry, McGill University, Montreal, Canada.)ANNALS OF MEDICINE, (1995 Dec) 27 (6) 663-70. Ref: 89. Journal code: AMD. ISSN: 0785-3890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB ***Apolipoprotein*** E (***apoE***) has been studied extensively with regard to its role in plasma lipoprotein lipid transport. A role for ***apoE*** in the transport of membrane cholesterol and phospholipid in the central and peripheral nervous system has also been studied. Entorhinal cortex-lesioned rats have been used extensively to examine the molecular mechanisms associated with deafferentation and reinnervation in the CNS; studies of the role of ***apoE*** in this process using this animal model are described. In all human populations examined, three common ***apoE*** isoforms, ***apoE2*** , ***apoE3*** and ***apoE4*** , result from multiple alleles epsilon 2, epsilon 3 and epsilon 4 at a single ***apoE*** genetic locus. These isoforms impart well-characterized functional differences in plasma lipoprotein transport, which are reviewed herein. Also discussed are less well-studied possible ***apoE*** -isoform specific differences in central nervous system function. These are currently of critical importance due to numerous recent studies showing an association of epsilon 4 with increased risk for Alzheimer's disease. Diverse hypotheses as to the molecular basis for this association, as well as the supporting experimental evidence, are reviewed.

L5 ANSWER 5 OF 13 MEDLINE

96217374 ***Apolipoprotein*** E and low-density lipoprotein binding and internalization in primary cultures of rat astrocytes: isoform-specific alterations. Guillaume D; Bertrand P; Dea D; Davignon J; ***Poirier J*** . (Douglas Hospital Research Centre, Department of Psychiatry and Neurology, McGill University, Verdun, Quebec, Canada.)JOURNAL OF NEUROCHEMISTRY, (1996 Jun) 66 (6) 2410-8. Journal code: JAV. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB ***Apolipoprotein*** (apo) E is likely involved in redistributing cholesterol and phospholipids during compensatory synaptogenesis in the injured CNS. Three common isoforms of ***apoE*** exist in human (E2, E3, and E4). The ***apoE4*** allele frequency is markedly increased in both late-onset sporadic and familial Alzheimer's disease (AD). ***ApoE*** concentration in the brain of AD subjects follows a gradient: ***ApoE*** levels decrease as a function of E2 > E3 >> E4. It has been proposed that the poor reinnervation capacity reported in AD may be caused by impairment of the ***apoE*** /low-density lipoprotein (LDL) receptor activity. To understand further the role of this particular axis in lipid homeostasis in the CNS, we have characterized binding, internalization, and degradation of human 125I-LDL to primary cultures of rat astrocytes. Specific binding was saturable, with a KD of 1.8 nM and a Bmax of 0.14 pmol/mg of proteins. Excess unlabeled human LDL or very LDL (VLDL) displaced 70% of total binding. Studies at 37 degrees C confirmed that astrocytes bind, internalize, and degrade 125I-LDL by a specific, saturable mechanism. Reconstituted ***apoE*** (E2, E3, and E4)-liposomes were labeled with 125I and incubated with primary cultures of rat astrocytes and hippocampal neurons to examine specific binding. Human LDL and VLDL displaced binding and internalization of all

apoE isoforms similarly in both astrocytes and neurons. 125I- ***ApoE2*** binding was significantly lower than that of the other 125I- ***apoE*** isoforms in both cell types. 125I- ***ApoE4*** binding was similar to that of 125I- ***apoE3*** in both astrocytes and neurons. On the other hand, 125I- ***apoE3*** binding was significantly higher in neurons than in astrocytes. These isoform-specific alterations in ***apoE*** -lipoprotein pathway could explain some of the differences reported in the pathophysiology of AD subjects carrying different ***apoE*** alleles.

L5 ANSWER 6 OF 13 MEDLINE
96187014 ***Apolipoprotein*** E, plaques, tangles and cholinergic dysfunction in Alzheimer's disease. Beffert U; ***Poirier J*** . (Department of Neurology and Neurosurgery, McGill University, Verdun, PQ, Canada.)ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1996 Jan 17) 777 166-74. Journal code: 5NM. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB ***Apolipoprotein*** E is a plasma cholesterol and phospholipid transporter which plays a central role in lipoprotein metabolism in the brain. ***Apolipoprotein*** E is a polymorphic protein with three common alleles in the general population, designated epsilon 2, epsilon 3 and epsilon 4 coding for proteins ***ApoE2*** , ***ApoE3*** and ***ApoE4*** , respectively. Recent findings have demonstrated a significant relationship between the epsilon 4 allele and late onset familial and sporadic Alzheimer's disease. We examined several classical neuropathological hallmarks of Alzheimer's disease to determine whether they might be related to ***apolipoprotein*** E genotype: the presence of intracellular neurofibrillary tangles, extracellular senile plaques, and the attenuation of choline acetyltransferase activity. Significant correlations were found between epsilon 4 allele copy number and senile plaque density in the frontal, parietal and fusiform cortical areas. Similarly, significant correlations were also found with increased neurofibrillary tangle number in the frontal and fusiform cortex. Interestingly, there was an inverse correlation between the epsilon 4 allele with temporal cortical choline acetyltransferase activity. To further define the specific function of ***ApoE4*** , cultured rat hippocampal neurons were used to investigate interactions involving beta-amyloid protein. In this model, ***ApoE4*** (but not ***ApoE2***) was able to reverse the neuroprotective effects of beta-amyloid. ***ApoE3*** was demonstrated to increase the internalization of beta-amyloid peptide into these neurons. Taken together, these results support the involvement of ***ApoE4*** in the pathogenesis of Alzheimer's disease and also provide some explanations for the possible function of this protein.

L5 ANSWER 7 OF 13 MEDLINE
96109245 ***Apolipoprotein*** E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. ***Poirier J*** ; Delisle M C; Quirion R; Aubert I; Farlow M; Lahiri D; Hui S; Bertrand P; Nalbantoglu J; Gilfix B M; et al. (McGill Centre for Studies in Aging, McGill University, Montreal, QC Canada.)PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Dec 19) 92 (26) 12260-4. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB ***Apolipoprotein*** E (***apoE***) is critical in the

modulation of cholesterol and phospholipid transport between cells of different types. Human ***apoE*** is a polymorphic protein with three common alleles, APO epsilon 2, APO epsilon 3, and APO epsilon 4. ***ApoE4*** is associated with sporadic and late-onset familial Alzheimer disease (AD). Gene dose was shown to have an effect on risk of developing AD, age of onset, accumulation of senile plaques in the brain, and reduction of choline acetyltransferase (ChAT) activity in the hippocampus of AD subjects. To characterize the possible impact of the ***apoE4*** allele on cholinergic markers in AD, we examined the effect of ***apoE4*** allele copy number on pre- and postsynaptic markers of cholinergic activity. ***ApoE4*** allele copy number showed an inverse relationship with residual brain ChAT activity and nicotinic receptor binding sites in both the hippocampal formation and the temporal cortex of AD subjects. AD cases lacking the ***apoE4*** allele showed ChAT activities close or within age-matched normal control values. The effect of the ***apoE4*** allele on cholinomimetic drug responsiveness was assessed next in a group (n = 40) of AD patients who completed a double-blind, 30-week clinical trial of the cholinesterase inhibitor tacrine. Results showed that > 80% of ***apoE4*** -negative AD patients showed marked improvement after 30 weeks as measured by the AD assessment scale (ADAS), whereas 60% of ***apoE4*** carriers had ADAS scores that were worse compared to baseline. These results strongly support the concept that ***apoE4*** plays a crucial role in the cholinergic dysfunction associated with AD and may be a prognostic indicator of poor response to therapy with acetylcholinesterase inhibitors in AD patients.

L5 ANSWER 8 OF 13 MEDLINE
95167718 ***Apolipoprotein*** E in animal models of CNS injury and in Alzheimer's disease. ***Poirier J*** . (McGill Center for Studies in Aging, Douglas Hospital Research Center, Quebec, Canada..)TRENDS IN NEUROSCIENCES, (1994 Dec) 17 (12) 525-30. Ref: 56. Journal code: WEL. ISSN: 0166-2236. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Recent evidence indicates that ***apolipoprotein*** E (***ApoE***) plays a central role in the hippocampal response to injury. The co-ordinated expression of ***ApoE*** and its receptor, the ***ApoE*** /ApoB [low density lipoprotein (LDL)] receptor, appears to regulate the transport of cholesterol and phospholipids during the early and intermediate phases of the reinnervation process. During dendritic remodeling and synaptogenesis, neurons progressively repress the synthesis of cholesterol in favor of cholesterol internalization through the ***ApoE*** /LDL receptor pathway. The discovery that the epsilon 4 allele is strongly linked to both sporadic and familial late-onset Alzheimer's disease (AD) raises the possibility that a dysfunction of the lipid-transport system associated with compensatory sprouting and synaptic remodeling could be central to the AD process. The role of ***ApoE*** in the CNS is particularly important in relation to the function of the cholinergic system, which relies to a certain extent on the integrity of phospholipid homeostasis in neurons. Recent evidence suggests that the epsilon 4 allele has a direct impact on cholinergic function in AD.

L5 ANSWER 9 OF 13 MEDLINE
95091460 Predictive value of ***apolipoprotein*** E genotyping in Alzheimer's disease: results of an autopsy series and an analysis of several combined studies. Nalbantoglu J; Gilfix B M; Bertrand P;

Robitaille Y; Gauthier S; Rosenblatt D S; ***Poirier J*** . (McGill Centre for Studies in Aging, Verdun, Quebec, Canada..)ANNALS OF NEUROLOGY, (1994 Dec) 36 (6) 889-95. Journal code: 6AE. ISSN: 0364-5134. Pub. country: United States. Language: English.

AB Apoliprotein E (***apoE***) is associated with Alzheimer's neurofibrillary tangles and beta-amyloid protein in senile plaques. Recent studies have shown an increased frequency of the epsilon 4 allele of the ***apoE*** gene in familial and sporadic cases of Alzheimer's disease (AD). In the present case control study, we have determined the ***apoE*** genotype by allele-specific extension of 113 postmortem cases of sporadic AD and 77 control brains shown to be free of AD neuropathological features and then calculated the frequency of the various allelic forms of ***apoE*** (epsilon 2, epsilon 3, epsilon 4). The odds ratio associating epsilon 4 with AD was 15.5 (95% confidence interval [CI] 6.2-38.5), and the population attributable risk was 0.53. We have also combined the results of our study and several others to calculate these same parameters in a larger population (570 controls and 961 AD subjects); the odds ratio for this larger group was 6.2 (95% CI 4.9-7.8) and the population attributable risk was 0.57. These results further substantiate and strengthen the association between the epsilon 4 allele of ***apoE*** gene and AD. We have also used these results to investigate the usefulness of the determination of epsilon 4 carrier status in the diagnosis of AD.

L17 ANSWER 15 OF 18 MEDLINE
96074266 Statement on use of ***apolipoprotein*** E testing for ***Alzheimer*** ***disease*** . American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and ***Alzheimer*** ***disease*** . Anonymous. JAMA, (1995 Nov 22-29) 274 (20) 1627-9. Ref: 55. Journal code: KFR. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB OBJECTIVE--To evaluate the published data on the association between ***apolipoprotein*** E genotype (APOE) and ***Alzheimer*** ***disease*** (AD) and determine whether the data support the use of genetic testing for ***diagnosis*** or prediction of disease. This statement is intended for neurologists, psychiatrists, geneticists, primary care providers, ***diagnostic*** laboratories, and the public. PARTICIPANTS--The joint American College of Medical Genetics (ACMG) and American Society of Human Genetics (ASHG) Test and Technology Transfer Committee developed a 10-member ACMG/ASHG Working Group to assess available data on the association of AD with APOE alleles. To ensure inclusion of clinical specialists primarily involved with AD patients and families, the American Academy of Neurology (AAN) and the American Psychiatric Association (APA) appointed liaisons to the Working Group. EVIDENCE--Peer-reviewed journal publications obtained from an Index Medicus search or known to members of the Working Group were the source of data on which the statement is based. CONSENSUS PROCESS--Following discussions with all members of the Working Group, a draft statement was prepared by the chair and circulated among all members until a consensus was reached. The consensus draft was sequentially reviewed and endorsed by the appropriate scientific and executive committees of the ACMG, ASHG, AAN, APA, and the National Institutes of Health-Department of Education Working Group on Ethical, Legal, and Social Implications of Human Genome Research. In some instances, suggestions from these committees were incorporated into the final statement. CONCLUSIONS--There is general consensus that APOE epsilon 4 is strongly associated with AD and

that when present may represent an important risk factor for the disease. However, at the present time it is not recommended for use in routine clinical ***diagnosis*** nor should it be used for predictive testing. Studies to date indicate that the APOE genotype alone does not provide sufficient sensitivity or specificity to allow genotyping to be used as a ***diagnostic*** test. Because AD develops in the absence of APOE epsilon 4 and because many with APOE epsilon 4 seem to escape disease, genotyping is also not recommended for use as a predictive genetic test. The results of a collaborative study under way will clarify some of these issues. Whether APOE genotypes have other uses in the management of AD will become apparent over the next few years.

L17 ANSWER 14 OF 18 MEDLINE
96109245 ***Apolipoprotein*** E4 allele as a predictor of cholinergic deficits and treatment outcome in ***Alzheimer*** ***disease*** . Poirier J; Delisle M C; Quirion R; Aubert I; Farlow M; Lahiri D; Hui S; Bertrand P; Nalbantoglu J; Gilfix B M; et al. (McGill Centre for Studies in Aging, McGill University, Montreal, QC Canada.)PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Dec 19) 92 (26) 12260-4. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB ***Apolipoprotein*** E (apoE) is critical in the modulation of cholesterol and phospholipid transport between cells of different types. Human apoE is a polymorphic protein with three common alleles, APO epsilon 2, APO epsilon 3, and APO epsilon 4. ApoE4 is associated with sporadic and late-onset familial ***Alzheimer*** ***disease*** (AD). Gene dose was shown to have an effect on risk of developing AD, age of onset, accumulation of senile plaques in the brain, and reduction of choline acetyltransferase (ChAT) activity in the hippocampus of AD subjects. To characterize the possible impact of the apoE4 allele on cholinergic markers in AD, we examined the effect of apoE4 allele copy number on pre- and postsynaptic markers of cholinergic activity. ApoE4 allele copy number showed an inverse relationship with residual brain ChAT activity and nicotinic receptor binding sites in both the hippocampal formation and the temporal cortex of AD subjects. AD cases lacking the apoE4 allele showed ChAT activities close or within age-matched normal control values. The effect of the apoE4 allele on cholinomimetic drug responsiveness was assessed next in a group (n = 40) of AD patients who completed a double-blind, 30-week clinical trial of the cholinesterase inhibitor tacrine. Results showed that > 80% of apoE4-negative AD patients showed marked improvement after 30 weeks as measured by the AD assessment scale (ADAS), whereas 60% of apoE4 carriers had ADAS scores that were worse compared to baseline. These results strongly support the concept that apoE4 plays a crucial role in the cholinergic dysfunction associated with AD and may be a ***prognostic*** indicator of poor response to therapy with acetylcholinesterase inhibitors in AD patients.

L17 ANSWER 10 OF 18 MEDLINE
97011173 ***Apolipoprotein*** E in neurology. Roses A D. (Alzheimer's Disease Research Center, Department of Medicine (Neurology), Duke University Medical Center, Durham, North Carolina 27110-2900, USA.)CURRENT OPINION IN NEUROLOGY, (1996 Aug) 9 (4) 265-70. Ref: 63. Journal code: BX4. ISSN: 1350-7540. Pub. country: United States. Language: English.

AB ***Apolipoprotein*** E became relevant for neurologists in 1993 when the association of the ***apolipoprotein*** E-epsilon 4 allele with familial and sporadic late-onset ***Alzheimer*** ***disease*** was reported. Since that time, more than 100 confirmations and many research papers have appeared. A large neurobiological literature concerning the role of ***apolipoprotein*** E in the metabolism of the central nervous system is developing.

L17 ANSWER 4 OF 18 MEDLINE
97205210 Exploring the etiology of ***Alzheimer*** ***disease*** using molecular genetics. Lendon C L; Ashall F; Goate A M. (Department of Psychiatry, Washington University School of Medicine, St Louis, MO 63110, USA.)JAMA, (1997 Mar 12) 277 (10) 825-31. Ref: 130. Journal code: KFR. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB ***Alzheimer*** ***disease*** (AD), the most common cause of dementia in the elderly, exists in both familial and sporadic forms. Genetic studies have led to the identification of 3 genes, beta-amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2), which, when mutated, can cause familial forms of AD. Mutations in each of these genes result in elevated levels of A beta42/43, a proteolytic processing fragment of APP that is deposited in brains of AD patients. Transgenic mice carrying AD-causing mutations in APP develop spontaneous age-related beta-amyloid (A beta) deposition and memory impairment. Genetic linkage and association studies have also shown that the epsilon4 allele of the ***apolipoprotein*** E (APOE) gene increases risk for AD in a dose-dependent manner in both familial and sporadic forms of AD and may account for as much as 50% of the attributable risk. APOE genotyping may be useful both as an adjunct to ***diagnosis*** and in identifying patient groups for therapeutic intervention. While the biological basis for the association of APOE epsilon4 with AD is not known, age of onset and A beta deposition are positively correlated with epsilon4 allele dosage in some cases, suggesting that this risk may also be mediated directly or indirectly through A beta. Because 50% of AD cases have no APOE epsilon4 alleles and families showing mendelian inheritance of AD exist in whom there are no mutations in any of the APP, PS1, or PS2 genes, it is likely that there are additional AD risk factors, both genetic and environmental, still to be identified.

L33 ANSWER 3 OF 3 MEDLINE
95057605 The apolipoprotein E alleles as major susceptibility factors for Creutzfeldt-Jakob disease. The French Research Group on Epidemiology of Human Spongiform Encephalopathies [see comments]. Amouyel P; Vidal O; Launay J M; Laplanche J L. (Service d'Epidemiologie, Institut Pasteur de Lille, France..)LANCET, (1994 Nov 12) 344 (8933) 1315-8. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Creutzfeldt-Jakob disease (CJD) is a rapid progressive mental and neurological disorder characterised by dementia and is both infectious and genetic. Pathogenic mutations and a predisposing polymorphism have been described in the ***prion*** protein gene and an abnormal ***prion*** product accumulates in the brain of affected patients. Apolipoprotein E (***APOE***), a protein of lipid metabolism, has been detected in some ***prion*** protein deposits. This ***ApoE*** exists as three common isoforms, coded by specific allele (epsilon 2, epsilon 3, epsilon 4). The presence

of at least one epsilon 4 allele was described as a major risk factor for Alzheimer's disease, another neurodegenerative disorder. From a series of 61 patients with CJD we found that epsilon 4 allele of the ***APOE*** gene was a risk factor for the disease ($p < 0.01$). This association was observed in both definite and probable cases, and for patients with and without ***prion*** protein gene mutations. Moreover, in affected subjects, epsilon 2 allele of the ***APOE*** gene delayed occurrence of death ($p < 0.01$) independently of other known mutations influencing the phenotype of the disease. These effects on neurodegenerative disease associated with ***APOE*** alleles suggest a strong involvement of the ***APOE*** locus in brain metabolism.

L33 ANSWER 1 OF 3 MEDLINE
97324027 Alpha1 antichymotrypsin signal peptide polymorphism in sporadic Creutzfeldt-Jakob disease. Salvatore M; Seeber A C; Nacmias B; Petraroli R; Sorbi S; Pocchiari M. (Laboratory of Virology, Istituto Superiore di Sanita, Rome, Italy.)NEUROSCIENCE LETTERS, (1997 May 16) 227 (2) 140-2. Journal code: N7N. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB In Creutzfeldt-Jakob disease (CJD), a transmissible spongiform encephalopathy, the deposition of the pathological ***prion*** protein (PrP-res) in the brain of affected individuals is the key event that triggers the appearance of the disease. Since a polymorphism in the signal peptide of the serine-protease inhibitor alpha1 antichymotrypsin (ACT) is one of the factors that may enhance amyloid formation, we studied this polymorphism in 63 CJD patients and 103 control subjects. No difference in allele frequencies and genotype distribution was found between CJD cases and controls, nor any difference was found between the ACT genotype and the age at onset and disease duration. Interestingly, there was a significantly different ($P = 0.04$) ACT distribution between CJD patients and controls in apolipoprotein E (***ApoE***) E4, and the interaction between ACT and ***ApoE*** was almost significant ($P = 0.053$). Further studies on a larger number of patients will clarify whether this association can identify a possible risk factor for CJD.

L33 ANSWER 2 OF 3 MEDLINE
96336003 Scrapie in mice deficient in apolipoprotein E or glial fibrillary acidic protein. Tatzelt J; Maeda N; Pekny M; Yang S L; Betsholtz C; Eliasson C; Cayetano J; Camerino A P; DeArmond S J; Prusiner S B. (Department of Neurology, University of California, San Francisco 94143-0518, USA.)NEUROLOGY, (1996 Aug) 47 (2) 449-53. Journal code: NZ0. ISSN: 0028-3878. Pub. country: United States. Language: English.

AB In the ***prion*** diseases, extensive reactive gliosis is often found to be out of proportion to the degree of apparent neuronal damage. To evaluate the role of astrocytic gliosis in experimental scrapie of the mouse, we inoculated mice deficient in apolipoprotein E (***apoE***) or the glial fibrillary acidic protein (GFAP) with mouse ***prions*** . The expression of both ***apoE*** and GFAP in astrocytes increases as part of the reactive gliosis that accompanies scrapie. Null mice deficient in either ***apoE*** or GFAP inoculated with ***prions*** exhibited incubation times indistinguishable from untargeted control mice. The level of PrPSc and its regional deposition in the brains of ill mice deficient in either protein were also similar to control mice. Our findings demonstrate that neither ***apoE*** nor GFAP participates in the

pathogenesis of the disease or in the production of PrPSc.

L37 ANSWER 4 OF 6 MEDLINE
96156461 Apolipoprotein E in sporadic and familial ***Creutzfeldt*** - ***Jakob*** disease. Salvatore M; Seeber A C; Nacmias B; Petraroli R; D'Alessandro M; Sorbi S; Pocchiari M. (Laboratory of Virology, Istituto Superiore di Sanita, Rome, Italy.)NEUROSCIENCE LETTERS, (1995 Oct 20) 199 (2) 95-8. Journal code: N7N. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB We assessed the apolipoprotein E (***ApoE***) genotype in 49 sporadic and ten familial ***Creutzfeldt*** - ***Jakob*** disease (CJD) patients, in seven healthy siblings with a PRNP mutation and in 84 controls. In sporadic CJD, ***ApoE*** genotypes and allelic frequencies do not significantly differ from that of controls. No influence of ***ApoE*** genotypes on age at onset was found. In familial cases, the disease appeared in mutated subjects showing the same ***ApoE*** genotype as members who have not yet developed CJD. Our results provide further evidence that ***ApoE*** is not a risk factor for CJD.

L57 ANSWER 1 OF 1 MEDLINE
94123654 Complex genetic disease: can genetic strategies in Alzheimer's disease and new genetic mechanisms be applied to epilepsy?. Roses A D; Pericak-Vance M A; Saunders A M; Schmechel D; Goldgaber D; Strittmatter W. (Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Department of Medicine (Neurology), Duke University Medical Center, Durham, North Carolina 27710-2900..)EPILEPSIA, (1994) 35 Suppl 1 S20-8. Ref: 76. Journal code: EIX. ISSN: 0013-9580. Pub. country: United States. Language: English.

AB Strategies used in molecular genetics have changed modern neurology. The gene or genes responsible for several major neurologic diseases have now been identified using "reverse" or positional genetics. Unexpected new genetic mechanisms have been discovered in human neurologic diseases, including (a) identical mutations of the prion protein gene in Creutzfeldt-Jakob disease and fatal familial insomnia with the phenotypic expression directed by an accompanying polymorphism; (b) stable duplications of chromosome 17 in Charcot-Marie-Tooth disease (type 1A) that involve many genes, only one of which appears to cause neuropathy; and (c) highly variable, dynamic mutations in myotonic dystrophy, ***fragile*** ***X*** ***syndrome*** , and Kennedy's syndrome that modulate variable expressivity in multiple tissues. There is growing recognition that neurologic diseases are often complex genetic diseases with multifactorial rather than simple modes of inheritance. For example, genetic association/linkage strategies have interacted with biochemistry and immunopathology studies to produce new insights into the disease mechanism of late-onset Alzheimer's disease. The role of ***apolipoprotein*** E in late-onset Alzheimer's disease is an example of how new analytical techniques of genetic disease can be applied to dissect multiple genes. Similar research strategies are suggested for the study of epilepsy as a complex disease.

L69 ANSWER 5 OF 14 MEDLINE
96364700 Ethical, social and legal issues in ***Huntington*** ***disease*** : the nurse's role. Rohs G; Klimek M L. AXONE, (1996 Mar) 17 (3) 55-9. Ref: 19. Journal code: AXO. ISSN: 0834-7824. Pub. country: Canada. Language: English.

AB The nurse's role will be discussed in relation to the issues which may present as the result of our ability to use predictive tests for neurodegenerative disease. ***Huntington*** ***disease*** is an autosomal dominant inherited disease, characterised by emotional problems, abnormalities of movement and dementia. The disease is slowly progressive leading to a severely debilitated state and finally death in ten to twenty years. In 1983, DNA testing became available for persons at risk for ***Huntington*** ***disease*** and for confirmation of diagnosis for those showing symptoms. The availability of testing presents many ethical, social and legal issues for persons at risk, health care professionals and other segments of society. This paper will briefly ***review*** the genetic transmission and profession of ***Huntington*** ***disease*** . It will outline some of the benefits as well as some of the risks and problems DNA testing presents.

L77 ANSWER 1 OF 7 MEDLINE
97354990 ***Huntington*** ***disease*** : advances in molecular and cell biology. Jones A L; Wood J D; Harper P S. (Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff, UK.)JOURNAL OF INHERITED METABOLIC DISEASE, (1997 Jun) 20 (2) 125-38. Ref: 71. Journal code: KY8. ISSN: 0141-8955. Pub. country: Netherlands. Language: English.

AB ***Huntington*** ***disease*** is an inherited neurodegeneration, for which the associated mutation was isolated in 1993. The mutation is an expansion of a CAG trinucleotide repeat, which translates to give a polyglutamine tract at the N-terminus of a large protein, huntingtin. Neither the normal nor the pathogenic functions of this protein have been identified, but it is clear that ***pathogenesis*** is mediated through the expanded polyglutamine tract within the protein, and that polyglutamine is toxic to cells. A number of proteins which interact with the N-terminal region of huntingtin have been isolated, but this has not, so far, yielded a rationale for ***pathogenesis*** . Huntingtin is found in areas of the brain that degenerate in this disease but is also associated with pathogenic inclusions in Alzheimer disease and Pick disease. It is possible that ***Huntington*** ***disease*** has pathogenic mechanisms in common with these other neurodegenerative diseases, and that the mechanism may relate to the formation of abnormal, cytoskeletal-associated, inclusions within cells.

L77 ANSWER 4 OF 7 MEDLINE
95350220 Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates. Brouillet E; Hantraye P; Ferrante R J; Dolan R; Leroy-Willig A; Kowall N W; Beal M F. (Departement de Recherche en Imagerie, Pharmacologie, et Physiologie, Commissariat `a la Energie Atomique-Direction des Sciences du Vivant, Orsay, France..)PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jul 18) 92 (15) 7105-9. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Although the gene defect responsible for ***Huntington*** ***disease*** (HD) has recently been identified, the ***pathogenesis*** of the disease remains obscure. One potential mechanism is that the gene defect may lead to an impairment of energy metabolism followed by slow excitotoxic neuronal injury. In the present study we examined whether chronic administration of 3-nitropropionic acid (3-NP), an irreversible inhibitor of succinate dehydrogenase, can replicate the neuropathologic and clinical

features of HD in nonhuman primates. After 3-6 weeks of 3-NP administration, apomorphine treatment induced a significant increase in motor activity as compared with saline-treated controls. Animals showed both choreiform movements, as well as foot and limb dystonia, which are characteristic of HD. More prolonged 3-NP treatment in two additional primates resulted in spontaneous dystonia and dyskinesia accompanied by lesions in the caudate and putamen seen by magnetic resonance imaging. Histologic evaluation showed that there was a depletion of calbindin neurons, astrogliosis, sparing of NADPH-diaphorase neurons, and growth-related proliferative changes in dendrites of spiny neurons similar to changes in HD. The striosomal organization of the striatum and the nucleus accumbens were spared. These findings show that chronic administration of 3-NP to nonhuman primates can replicate many of the characteristic motor and histologic features of HD, further strengthening the possibility that a subtle impairment of energy metabolism may play a role in its ***pathogenesis*** .

L73 ANSWER 4 OF 46 MEDLINE
97156073 Trinucleotide repeat disorders in humans: discussions of mechanisms and medical issues. Timchenko L T; Caskey C T. (Department of Medicine, Section of Cardiology, Baylor College of Medicine, Houston, Texas 77030, USA.)FASEB JOURNAL, (1996 Dec) 10 (14) 1589-97. Ref: 70. Journal code: FAS. ISSN: 0892-6638. Pub. country: United States. Language: English.

L81 ANSWER 15 OF 15 MEDLINE
96174709 Genetic association between intronic polymorphism in ***presenilin*** -1 gene and late-onset Alzheimer's disease. Alzheimer's Disease Collaborative Group [see comments]. Wragg M; Hutton M; Talbot C. (Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA.)LANCET, (1996 Feb 24) 347 (9000) 509-12. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Mutations in the ***presenilin*** -1 (PS-1) gene are associated with early-onset Alzheimer's disease. 40-50% of the risk for late-onset disease has been attributed to alleles at the apolipoprotein E (***ApoE***) locus. We have looked for an association between PS-1 and late- onset disease. METHODS: We collected blood samples from 208 white cases of dementia of the Alzheimer type and from 185 age-matched controls (mean ages 76.9 and 76.2 years, respectively; 58% female in each series). Clinical diagnostic accuracy for Alzheimer's disease in our patients is 96%. We also studied 29 African-American patients with dementia of the Alzheimer type and 50 age-matched controls (cases vs controls, 77.2 vs 72.0 years; 72 vs 77% female). We used PCR to test for an association between Alzheimer's disease and a polymorphism within the intron 3' to exon 8 of the PS-1 gene. The ***ApoE*** genotype of most of the cases and controls was known from previous investigations. FINDINGS: Homozygosity of the 1 allele in the PS-1 gene was associated with a doubling of the risk for late-onset Alzheimer's disease compared with the [12]/[22] genotype (odds ratio 1.97, 95% Cl 1.29-3.00). The proportion of Alzheimer's disease cases in the white population that could be attributed to homozygosity at this locus, as estimated by the attributable fraction, was 0.22. This compares with 0.35 for a single copy of ***ApoE4*** and 0.15 for two copies. The smaller African-American series showed similar distribution of PS-1 genotype between cases and controls. INTERPRETATION: In our white series of cases, PS-1 accounted for about half as much of the risk for late-onset Alzheimer's disease as

L81 ANSWER 13 OF 15 MEDLINE
96414307 Alzheimer's disease associated with mutations in ***presenilin*** 2 is rare and variably penetrant. Sherrington R; Froelich S; Sorbi S; Campion D; Chi H; Rogaeva E A; Levesque G; Rogaev E I; Lin C; Liang Y; Ikeda M; Mar L; Brice A; Agid Y; Percy M E; Clerget-Darpoux F; Piacentini S; Marcon G; Nacmias B; Amaducci L; Frebourg T; Lannfelt L; Rommens J M; St George-Hyslop P H. (Department of Medicine, University of Toronto, Ontario, Canada.)HUMAN MOLECULAR GENETICS, (1996 Jul) 5 (7) 985-8. Journal code: BRC. ISSN: 0964-6906. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Missense mutations in the ***presenilin*** 2 (PS-2) gene on chromosome 1 were sought by direct nucleotide sequence analysis of the open reading frame of 60 pedigrees with familial Alzheimer's disease (FAD). In the majority of these pedigrees, PS-1 and beta-amyloid precursor protein (beta APP) gene mutations had been excluded. While no additional PS-2 pathogenic mutations were detected, four silent nucleotide substitutions and alternative splicing of nucleotides 1338-1340 (Glu325) were observed. Analysis of additional members of a pedigree known to segregate a Met239Val mutation in PS-2 revealed that the age of onset of symptoms is highly variable (range 45-88 years). This variability is not attributable to differences in ***ApoE*** genotypes. These results suggest (i) that, in contrast to mutations in PS-1, mutations in PS-2 are a relatively rare cause of FAD; (ii) that other genetic or environmental factor modify the AD phenotype associated with PS-2 mutations; and (iii) that still other FAD susceptibility genes remain to be identified.

L81 ANSWER 11 OF 15 MEDLINE
97061686 A ***presenilin*** 1 mutation in an early onset Alzheimer's family: no association with ***presenilin*** 2. Poduslo S E; Herring K; Neal M. (Department of Neurology, Texas Tech University, Health Sciences Center, Lubbock 79430, USA.)NEUROREPORT, (1996 Aug 12) 7 (12) 2018-20. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Genes on four chromosomes have been associated with Alzheimer's disease. Mutations in the chromosome 14 gene (S182 or ***presenilin*** 1) have been linked with an aggressive very early form of the disease while mutations in a chromosome 1 gene (STM2 or ***presenilin*** 2) have been linked with Volga German kindreds. When we screened our Alzheimer's patients for the first mutations reported, we only found one in the ***presenilin*** 1 gene in an extended family with three affected siblings, all of whom had onset of symptoms in their 4Cs. ***ApoE*** and ApoCI genotyping indicated that these risk factors were not associated with the disease in this family. None of our patients with early or late onset disease had the mutation described for ***presenilin*** 2.

L81 ANSWER 6 OF 15 MEDLINE
97205210 Exploring the etiology of Alzheimer disease using molecular genetics. Lendon C L; Ashall F; Goate A M. (Department of Psychiatry, Washington University School of Medicine, St Louis, MO 63110, USA.)JAMA, (1997 Mar 12) 277 (10) 825-31. Ref: 130. Journal code: KFR. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB Alzheimer disease (AD), the most common cause of dementia in the

elderly, exists in both familial and sporadic forms. Genetic studies have led to the identification of 3 genes, beta-amyloid precursor protein (APP), ***presenilin*** -1 (PS1), and ***presenilin*** -2 (PS2), which, when mutated, can cause familial forms of AD. Mutations in each of these genes result in elevated levels of A beta42/43, a proteolytic processing fragment of APP that is deposited in brains of AD patients. Transgenic mice carrying AD-causing mutations in APP develop spontaneous age-related beta-amyloid (A beta) deposition and memory impairment. Genetic linkage and association studies have also shown that the epsilon4 allele of the apolipoprotein E (***APOE***) gene increases risk for AD in a dose-dependent manner in both familial and sporadic forms of AD and may account for as much as 50% of the attributable risk. ***APOE*** genotyping may be useful both as an adjunct to diagnosis and in identifying patient groups for therapeutic intervention. While the biological basis for the association of ***APOE*** epsilon4 with AD is not known, age of onset and A beta deposition are positively correlated with epsilon4 allele dosage in some cases, suggesting that this risk may also be mediated directly or indirectly through A beta. Because 50% of AD cases have no ***APOE*** epsilon4 alleles and families showing mendelian inheritance of AD exist in whom there are no mutations in any of the APP, PS1, or PS2 genes, it is likely that there are additional AD risk factors, both genetic and environmental, still to be

L81 ANSWER 3 OF 15 MEDLINE
97325306 No association or linkage between an intronic polymorphism of ***presenilin*** -1 and sporadic or late-onset familial Alzheimer disease. Scott W K; Yamaoka L H; Locke P A; Rosi B L; Gaskell P C; Saunders A M; Conneally P M; Small G W; Farrer L A; Growdon J H; Roses A D; Pericak-Vance M A; Haines J L. (Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.)GENETIC EPIDEMIOLOGY, (1997) 14 (3) 307-15. Journal code: FMP. ISSN: 0741-0395. Pub. country: United States. Language: English.

AB Recent reports have shown an association between an intronic polymorphism of the ***presenilin*** -1 (PSEN1) gene and late-onset (age at onset > 65) familial and sporadic (no family history) Alzheimer disease (AD). The reported association was independent of the effect of the only previously identified gene associated with late-onset AD, ***APOE*** . Blood samples were obtained from members of 122 multiplex AD families, 42 unrelated cases of AD with positive family histories of dementia, 456 sporadic cases of AD, and 317 controls of similar ages at examination to the cases. These samples were genotyped for an intronic polymorphism of the PSEN1 gene, located 3' to exon 8, and the data analyzed for evidence of association or linkage. The samples were also genotyped for ***APOE*** and the data analyzed to see if the association or linkage changed when controlling for ***APOE*** genotype. There was no statistically significant increase (at alpha = .01) in allele 1 (199 bp) or genotype 1/1 in the sporadic AD cases, or in a random sample of one affected from each multiplex family, compared to controls. When examining the effect of the PSEN1 polymorphism while controlling for ***APOE*** genotype, ***APOE*** genotype was strongly associated with AD, but the PSEN1 polymorphism genotype was not. Model-trait dependent (lod score) and independent (Sim1BD) methods detected no evidence of linkage between PSEN1 and AD. In this independent dataset, the previously reported association between the intronic PSEN1 polymorphism and AD cannot be confirmed, and the conclusion that PSEN1 is a major susceptibility gene for late-onset AD is not supported.

L85 ANSWER 1 OF 1 MEDLINE
94175077 The ***apolipoprotein*** E/CI/CII gene cluster and late-onset ***Alzheimer*** ***disease*** . Yu C E; Payami H; Olson J M; Boehnke M; Wijsman E M; Orr H T; Kukull W A; Goddard K A; Nemens E; White J A; et al. (Division of Neurology, University of Washington, Seattle 98195.)AMERICAN JOURNAL OF HUMAN GENETICS, (1994 Apr) 54 (4) 631-42. Journal code: 3IM. ISSN: 0002-9297. Pub. country: United States. Language: English.

AB The chromosome 19 ***apolipoprotein*** E/CI/CII gene cluster was examined for evidence of linkage to a familial ***Alzheimer*** ***disease*** (FAD) locus. The family groups studied were Volga German (VG), early-onset non-VG (ENVG; mean age at onset < 60 years), and late-onset families. A genetic association was observed between ***apolipoprotein*** E (ApoE) allele epsilon 4 and FAD in late-onset families; the epsilon 4 allele frequency was .51 in affected subjects, .37 in at-risk subjects, .11 in spouses, and .19 in unrelated controls. The differences between the epsilon 4 frequencies in affected subjects versus controls and in at-risk subjects versus controls were highly significant (standard normal deviate [ZSND]) = 7.37, P < 10(-9); and ZSND = 4.07, P < .00005, respectively). No association between the epsilon 4 allele and FAD was observed in the ENVG or VG groups. A statistically significant allelic association between epsilon 4 and AD was also observed in a group of unrelated subjects; the epsilon 4 frequency was .26 in affected subjects, versus .19 in controls (ZSND = 2.20, P < .03). Evidence of linkage of ApoE and ***ApoCII*** to FAD was examined by maximum-likelihood methods, using three models and assuming autosomal dominant inheritance: (1) age-dependent penetrance, (2) extremely low (1%) penetrance, and (3) age-dependent penetrance corrected for sporadic ***Alzheimer*** ***disease*** (AD). For ***ApoCII*** in late-onset families, results for close linkage were negative, and only small positive lod-score-statistic (Z) values were obtained (model 1, maximum Z[Zmax] = 0.61, recombination fraction [theta] = .30; model 2, Zmax = 0.47, theta = .20). For ApoE in late-onset kindreds, positive Z values were obtained when either allele frequencies from controls (model 1, Zmax = 2.02, theta = .15; model 2, Zmax = 3.42, theta = .05) or allele frequencies from the families (model 1, Zmax = 1.43, theta = .15; model 2, Zmax = 1.70, theta = .05) were used. When linkage disequilibrium was incorporated into the analysis, the Z values increased (model 1, Zmax = 3.17, theta = .23; model 3, Zmax = 1.85, theta = .20). For the ENVG group, results for ApoE and ***ApoCII*** were uniformly negative. Affected-pedigree-member analysis gave significant results for the late-onset kindreds, for ApoE (ZSND = 3.003, P = .003) and ***ApoCII*** (ZSND = 2.319, P = .016), when control allele frequencies were used but not when allele frequencies were derived from the families.

L22 ANSWER 1 OF 1 USPATFULL
96:31717 Methods of screening for Alzheimer's disease.
Roses, Allen D., Durham, NC, United States
Strittmatter, Warren J., Durham, NC, United States
Salvesen, Guy S., Chapel Hill, NC, United States
Enghild, Jan, Durham, NC, United States
Schmechel, Donald E. , Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 5508167 960416
APPLICATION: US 94-227044 940413 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of diagnosing or prognosing Alzheimer's disease in a subject are disclosed. The methods involve directly or indirectly detecting the presence or absence of an apolipoprotein E type 4 (ApoE4) isoform or DNA, encoding ApoE4 in the subject. The presence of ApoE4 indicates the subject is afflicted with Alzheimer's disease or at risk of developing Alzheimer's disease. A novel immunochemical assay for detecting the presence or absence of the Apoliprotein E (ApoE) E4 allele in a subject is also disclosed.